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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,062	03/10/2004	Minoru Yamaguchi	OKA-0216	2613

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EXAMINER

HINES, JANA A

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1645

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/796,062	Applicant(s) YAMAGUCHI ET AL.	
	Examiner Ja-Na Hines	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Amendments

1. The amendment filed October 31, 2008 has been entered. Claims 1 and 8-10 have been amended. Claims 1-11 are under consideration in this office action.

Withdrawal of Objections and Rejections

2. The following objections and rejections have been withdrawn in view of applicants' amendments and/or arguments:
 - a) The objection to the disclosure;
 - b) The rejection of claim 8 under 35 U.S.C. 112, second paragraph,
 - c) The rejection of claims 1 and 9-11 under 35 U.S.C. 102(b) as being anticipated by Nakanishi et al., Publication Number 2001-235477, (published August 31, 2001).

Response to Arguments

3. Applicant's arguments filed October 31, 2008 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 1 recites the phrase "amino acid derivatives" however it is unclear how to define "derivatives". The derivative language is vague and indefinite because the characteristics needed to determine whether an unknown could be considered a derivative of an amino acid are unknown. The specification does not teach a requisite amount of retained qualities needed or characteristics necessary to determine amino acid derivatives. Therefore the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4 and 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Bauer et al., (2000. Rapid Comm. In Mass Spectrometry. Volume 14, Issue 10, Pages 924-929).

The claims are drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid derivative, said amino acid derivative being negatively charged as a whole molecule and comprising an amino acid having an amino group protected with a protective group and a side chain containing an

acidic group; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for coupling to said amino acid derivative; coupling said amino acid derivative to the N-terminus of the peptide of interest or the fragments thereof to obtain a coupled peptide molecule; and subjecting the coupled peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the peptide molecule determines the amino acid sequence of the peptide. Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claim 4 are drawn to the protective group; claim 8 is drawn to the hydrolysis of the C-terminal side; 9 is drawn to the ionization and decay of the peptide; claim 10 is drawn to the ionization by ionized by matrix-assisted laser desorption ionization (MALDI); and claim 11 is drawn to separation and detection by time-of-flight mass spectrometry (TOFMS).

Bauer et al., teach a method for determining amino acid sequence of a peptide, comprising: preparing a peptide of interest by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest, wherein the amino acid derivative having protected an amino group with a protective group and derived from an amino acid with a side chain containing an acidic group; and subjecting the coupled product to mass spectrometry analysis (abstract). Bauer et al., teach the model peptide was oxidized with performic acid to convert the cysteine to cysteic acid, was analyzed by mass spectrometry (page 925, col.1). Bauer et al., teach the sulfonic acid derivatization of the N-terminus using chlorosulfonylacetyl chloride and performic acid oxidation of cysteine were carried out (page 925, col. 1). Thereby Bauer et al., teach coupling the amino acid derivative to the peptide of interest. Bauer et al., teach the N-

terminal acid group being generated by converting the side chain of the cysteine to cysteic acid by exposure to performic acid (page 926, col. 1). The acidic group of cysteic acid is a sulfo group and the amino acid is cysteic acid. The use of highly acidic, N-terminal derivatives simplifies the interpretation of fragment ion spectra for peptide ions produced by ionization techniques (page 924, col. 2). Bauer et al., teach derivatization techniques has improved the quality of PSD-MADLI spectra (page 924, col.2).

Bauer et al., teach subjecting the derivatized product to mass spectrometry were the mass spectra provided peptide sequence interpretation (page 925, col.2). Mass spectrometry has become a standard approach for the identification and characterization of proteins (page 924, 926 col.1 and 2). Bauer et al., teach preparing a peptide of interest obtained by cleaving the peptide of interest wherein the derivatization procedure depends on derivatized tryptic digests of proteins (page 927, col.2). Bauer et al., teach sequence information is provided when techniques involve using a protease (page 924, col.1). Tryptic digests have the advantage of producing peptides possessing a basic residue at their C-terminus (page 924, col. 1). Therefore, Bauer et al., teach cleavage performed by the trypsin enzyme that specifically hydrolyzes a peptide bond on the C-terminal side of a basic amino acid residue.

Bauer et al., teach claims 1-4 and 8-11 of the instant application.

Response to Arguments

6. Applicants argue that Bauer et al., do not subject the peptide of interest to a coupling step and that Bauer et al., do not teach an amino acid derivative. However, Bauer et al., teach the sulfonic acid derivatization of the N-terminus using chlorosulfonylacetate and performic acid oxidation of cysteine were carried out. Thereby Bauer et al., teach coupling the sulfonic acid amino acid derivative to the peptide of interest, contrary to applicants' assertions. Therefore applicants' argument is not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

7. Claims 1-4 and 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Keough et al., (1999. PNAS Vol. 96:7131-7136).

Claim 1 is drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid derivative, said amino acid derivative being negatively charged as a whole molecule and comprising an amino acid having an amino group protected with a protective group and a side chain containing an acidic group; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for coupling to said amino acid derivative; coupling said amino acid derivative to the N-terminus of the peptide of interest or the fragments thereof to obtain a coupled peptide molecule; and subjecting the coupled peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the

peptide molecule determines the amino acid sequence of the peptide. Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claim 4 are drawn to the protective group; 9 is drawn to the ionization and decay of the peptide; claim 10 is drawn to the ionization by ionized by matrix-assisted laser desorption ionization (MALDI); and claim 11 is drawn to separation and detection by time-of-flight mass spectrometry (TOFMS).

Keough et al., teach a method for determining amino acid sequence of a peptide, comprising the steps of: preparing a peptide of interest obtained by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest wherein the amino acid derivative has a protected amino group with a protective group and derived from an amino acid with a side chain containing an acidic group; and subjecting the coupled product to mass spectrometry analysis (page 7132). Keough et al., teach a method involves the addition of a strong acid group (amino acid derivative) Keough et al., teach considerable enhancement of the N-terminal ion after enhancement which aided in the complete sequencing of the peptide (page 7133, col.1). Keough et al., teach procedures for high-sensitivity tryptic peptide sequencing using Matrix-Assisted Laser Desorption Ionization Spectrometry Post Source Decay (PSD MALDI) and routes to produce tryptic peptides containing an N-terminal sulfonic acid. The peptide of interest has been cleaved with a tryptic enzyme before coupling the N-terminus of the peptide.

Keough et al., teach the N-terminal derivatization procedures involve coupling an amino acid derivative to the N terminus of peptides (page 7132, col.1). This derivatization reaction introduces an aromatic sulfonic acid group directly at the N terminus of the peptide (page 7133, col.2). Keough et al., also teach peptides derivatized with carboxylic acids (page 7132, col.1). Therefore Keough et al., teach a derivative derived from an amino acid with a side chain containing an acidic group such as a sulfo group found on cysteic acid. Keough et al., teach the PSD MALDI analysis of a commercially available peptide, CDPGYIGSR (page 7133, col.1). Keough et al., also teach analysis with Time-of-Flight mass (TOF) spectrometry (page 7131, col.1). Keough et al., shows in the lower drawing of Fig. 1, an improved spectrum after oxidation of the N-terminal cysteine to cysteic acid and the complete sequence of the peptide could be determined by PSD MALDI after oxidation (page 7133, col. 1). Keough et al., teach that PSD MALDI mass spectrometry was developed for high-sensitivity peptide sequencing applications has become an increasingly essential tool for protein and peptide sequencing because of its speed, sensitivity, and applicability to analyze complex mixtures (page 7131, col.1).

Keough et al., teach claims 1-4 and 9-11 of the instant application.

Response to Arguments

8. Applicants argue that Keough et al., do not subject the peptide of interest to a coupling step and that Keough et al., do not teach an amino acid derivative. However, Keough et al., teach a method involves the addition or coupling of a strong acid group

(amino acid derivative). Keough et al., teach the peptide of interest was cleaved with a tryptic enzyme before coupling the N-terminus of the peptide. Keough et al., teach the N-terminal derivatization procedures involve coupling an amino acid derivative to the N terminus of peptides. Keough et al., teach a derivatization reaction that introduces an aromatic sulfonic acid group directly at the N terminus of the peptide. Keough et al., teach peptides derivatized with carboxylic acids. Therefore Keough et al., teach a derivative derived from an amino acid with a side chain containing an acidic group such as a sulfo group found on cysteic acid. Therefore applicants' argument is not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turecek (2002. J. Mass Spectrometry. Vol. 37:1-14) in view of Keough et al., (1999. PNAS Vol. 96:7131-7136).

Claim 1 is drawn to a method for determining amino acid sequence of a peptide, comprising the steps of: preparing an amino acid derivative, said amino acid derivative being negatively charged as a whole molecule and comprising an amino acid having an

amino group protected with a protective group and a side chain containing an acidic group; preparing a peptide of interest or fragments thereof obtained by optionally cleaving the peptide of interest for coupling to said amino acid derivative; coupling said amino acid derivative to the N-terminus of the peptide of interest or the fragments thereof to obtain a coupled peptide molecule; and subjecting the coupled peptide molecule to mass spectrometry analysis wherein the analysis of the mass spectra of the peptide molecule determines the amino acid sequence of the peptide. Claim 2 is drawn to the acidic group; claim 3 is drawn to the amino acid; claims 4-6 are drawn to the protective group; claim 7 is drawn to a N-biotinylcysteic acid; claim 8 is drawn to the hydrolysis of the C-terminal side; 9 is drawn to the ionization and decay of the peptide; claim 10 is drawn to the ionization by ionized by matrix-assisted laser desorption ionization (MALDI); and claim 11 is drawn to separation and detection by time-of-flight mass spectrometry (TOFMS).

Turecek teach a method for determining amino acid sequence of a peptide, comprising preparing a peptide of interest obtained by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest, the amino acid derivative having protected an amino group with a protective group and subjecting the coupled product to mass spectrometry analysis (see Figure 6 and Schemes 6 and 8). The Isotope-Coded Affinity Tags for protein (ICAT) analysis, wherein ICAT relies on *in vitro* derivatization with biotinylated tags on proteins, followed by matrix-assisted laser desorption ionization (MALDI) (page 8, col.2). Turecek teach peptide sequencing (page

10, col.1). Turecek teaches that derivatization ensures selective conjugation of the N-terminal cysteine or at N-terminal serine or threonine groups (page 8,col. 2). Turecek also teaches of cysteine-targeting affinity tags wherein following tryptic digestion, the biotin derivatives couple with cysteine (page 11, col.2).

Turecek teaches the N-terminal biotinylated proteins whose serine and threonine residues were targeted, followed by digestion and MALDI-TOFMS analysis (page 11-12, col.2-1). Turecek teaches that cysteines are derivatized with the biotin tag via the thiol specific reactive group (Figure 6). Turecek teaches the advantage of using the biotinylated cysteine tag to provide stronger yet reversible links (page 9, col.1). This selective affinity method simplifies the peptide mixture and does not interfere with the mass spectrometric MALDI-TOFMS analysis (page 9, col.2). Turecek teaches that common proteolytic enzymes such as trypsin does not interfere with the biotin label (page 9, col1). However Turecek does not teach the amino acid derivative being from an amino acid with a side chain containing an acidic group.

Keough et al., teach a method involves the addition of an amino acid derivative having a strong acid group (amino acid derivative) to the N terminus of tryptic peptides before MALDI analyses (page 7132, col.1). The N-terminal derivatization procedures involve coupling an amino acid derivative to the N terminus of peptides (page 7132, col.1). This reaction introduces an aromatic sulfonic acid group directly at the N terminus of the peptide (page 7133, col.2). Keough et al., teach MALDI procedures for high-sensitivity tryptic peptide sequencing to produce tryptic peptides containing an N-terminal sulfonic acid (page 7132, col.1). Therefore Keough et al., teach a derivative

derived from an amino acid with a side chain containing an acidic group such as a sulfo group found on cysteic acid (page 7132, col.1). Keough et al., show an improved spectrum after oxidation of the N-terminal cysteine to cysteic acid (page 7133, col. 1). Keough et al., teach considerable enhancement of the N-terminal ion after enhancement which aided in the complete sequencing of the peptide (page 7133, col.1).

Therefore it would have been prima facie obvious at the time of applicants invention to add of an amino acid derivative having a strong acid group to Turecek's method for determining amino acid sequence of a peptide, comprising preparing a peptide of interest obtained by cleaving the peptide of interest; coupling an amino acid derivative to the N-terminus of the peptide of interest, the amino acid derivative having protected an amino group with a protective group and subjecting the coupled product to mass spectrometry analysis in order to provide an improved mass spectrometric spectrum after oxidation to a cysteic acid. One of ordinary skill in the art would have a reasonable expectation of success modifying the method of determination as taught by Turecek because Turecek already teach that derivatization ensures selective conjugation of the N-terminal cysteine while protecting the amino group and Keough teach considerable enhancement within the mass spectra result. Furthermore, no more than routine skill would have been required to use an amino acid derivative with a side chain having an acidic group since Keough et al., this technique is well known to aide in the complete sequencing of the peptide using MALDI-TOF analysis.

Response to Arguments

10. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been prima facie obvious at the time of applicants' invention to add of an amino acid derivative being negatively charged as a whole molecule and comprising an amino acid having an amino group protected with a protective group and a side chain containing an acidic group to Turecek's method for determining amino acid sequence of a peptide in order to provide an improved mass spectrometric spectrum after oxidation to a cysteic acid.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, Turecek in view of Keough et al., teach that one of ordinary skill in the art would have a reasonable expectation of success modifying the method of determination as taught by Turecek because Turecek already teach that derivatization ensures selective conjugation of the N-terminal cysteine while protecting the amino group and

Keough teach considerable enhancement within the mass spectra result using an amino acid derivative being negatively charged as a whole molecule and comprising an amino acid having an amino group protected with a protective group and a side chain containing an acidic group. Therefore applicants' arguments are not persuasive and the rejection is maintained.

Conclusion

11. No claims allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

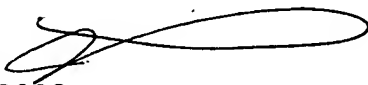
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13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines 
January 14, 2008


MARK NAVARRO
PRIMARY EXAMINER